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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/847,623	05/02/2001	Thomas Dyrberg	4401.214-US	6709

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EXAMINER	
CELSA, BENNETT M	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 04/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,8,9 and 11* is/are pending in the application.

4a) Of the above claim(s) *11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,8 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

4) ☐ Interview Summary (PTO-413)

3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)

5) ☐ Notice of Informal Patent Application (PTO-152)

DETAILED ACTION

Response to Amendment

Applicant's Jan. 20, 2004 amendment and further amendment of February 18, 2004 (in response to the Notice of Non-Compliant amendment) is hereby acknowledged.

Status of the Claims

Claims 6, 8, 9 and 11 are currently pending.

Claims 6 and 8-9 are under consideration to the extent they read on the elected invention.

Claim 11 is withdrawn from consideration as being directed to a nonelected invention.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

Applicant's election with traverse of AspB25 human insulin in Paper No. 5 (dated 6/30/03), which is asserted to read on claims 6 and 8-10, is again acknowledged. The requirement is still deemed proper and is therefore made FINAL.

This application contains claims 6,8,9 (in part) and 11 drawn to nonelected nonelected subject matter. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Withdrawn Objection (s) and/or Rejection (s)

Applicant's amendment and arguments have overcome the new matter rejection and indefinite rejections of claim 8 presented in the prior office action.

The rejection of claims 6, 8 and 9 are rejected under 35 U.S.C. 102(b) as anticipated by Affholter et al. Biochemistry Vol. 29 (33) (1990) pages 7727-7733 is withdrawn in view of applicant's amendment and arguments.

The rejection of claim 6, 8 and 9 as anticipated by Drejer is withdrawn in view of applicant's amendment.

New Objection (s) and/or Rejection (s)

Claims 6, 8 and 9 are rejected under 35 U.S.C. 102(b) as obvious over Drejer et al. Diabetes Vol. 40 (Nov. 1991) pages 1488-1495 in view of the specification (pages 9-11 and Table 1 to demonstrate inherent properties alone or further in view of Bakaysa et al. US 5,474,978 (12/95:filed 6/94), DeFilippis US 5,461,031 (10/95: filed 6/94) and/or Balschmidt WO 95/00550 (1/95).

The presently claimed invention is drawn to a "pharmaceutical composition" comprising:

a. AspB25 human insulin which is asserted to be a hormonally inactive insulin analogue (<7% of human insulin's activity in an in vitro fat cell or receptor binding assay);

b. "for treating or ameliorating type I diabetes" (intended use); and

c. "in an amount effective for said treating or ameliorating (type I diabetes)".

The Drejer et al. reference teaches the *in vitro* screening of 5 (five) human insulin analogs, including Asp B25 human insulin and Asp B28 human insulin with the

aim being: "to characterize five very different insulin analogues regarding their interaction with the insulin receptor in terms of binding affinity; kinetic properties, and ability to activate tyrosine kinase" which is a "prerequisite for investigations of the **in vivo activity of fast-acting analogues**" (e.g. see page 1488, especially right column: emphasis provided). Drejer et al. further concludes that "[T] he availability of analogues with a broad range of receptor affinities may enable us to reach a better understanding of the mechanism of insulin action" but "**[I] n particular, analogues with very low and very high affinity will continue to be valuable for in vitro and in vivo studies**" (see page 1494: bottom left column to top right column: emphasis provided).

The Drejer et al. reference clearly teaches compositions comprising an Asp B25 human insulin compound which inherently is a hormonally inactive insulin analogue (<7% of human insulin's activity in an in vitro fat cell or receptor binding assay) as demonstrated by applicant's own specification teaching that AspB25 possesses such characteristics. See e.g. specification pages 9-11 and Table 1.

To the extent that the presently claimed invention is drawn to a composition, intended use limitations (e.g. for treating or ameliorating type I diabetes) is not afforded patentable weight.

Turning to the new claim limitation requiring the presence of AspB25 "in an amount effective for said treating or ameliorating (type I diabetes)" it is noted that the specification on pages 14-16 (and examples) indicate pharmaceutical compositions "prepared by conventional techniques" for broad administration (e.g. orally/parenterally/transdermally) of analogs alone or in pH buffered solution (e.g. with

water, isotonic agents, preservative, auxiliary agents) without any indication of criticality regarding "effective amounts". The specification seems to indicate the non-criticality of analog amount which is effective to treat/ameliorate type 1 diabetes since no concentration amounts (or ranges) for various administration modes are disclosed.

In this regard, the Drejer et al. reference provides explicit motivation (as outlined above e.g. abstract; pages 1488 and 1494) for one of ordinary skill in the art utilizing conventional techniques to formulate pharmaceutical compositions comprising the Drejer insulin analogs, including Asp B25, in light of their expected value in *in vivo* studies, utilizing various amounts corresponding to various modes of administration (e.g. oral/parenteral/transdermal), especially for investigations involving the determination of these analogs for their **in vivo activity as fast-acting analogues** (emphasis provided).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to formulate pharmaceutical compositions comprising the Drejer insulin analogs, including Asp B25 in amounts within the scope of the presently claimed invention (e.g. "in an amount effective for said treating or ameliorating (type I diabetes)") in view of the non-criticality of the analog amount which is effective to treat/ameliorate type 1 diabetes.

Additionally, the prior art reference(s) need only to render obvious the claimed composition and it is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. In re Linter, 458 F.2d 1013, 173

USPQ 560 (CCPA 1972); In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990), cert. denied, 500 U.S. 904 (1991); MPEP 2144.

The Bakaysa et al. US 5,474,978 (12/95:filed 6/94), DeFilippis US 5,461,031 (10/95: filed 6/94) and/or Balschmidt WO 95/00550 (1/95) are all cited to demonstrate the making of pharmaceutical composition comprising fast-acting insulin analog Asp B28 disclosed in the Drejer reference in amounts and modes of administration within the scope of the presently claimed invention; including Asp B28 insulin analog in pH buffered solution (e.g. with water, iosotonic agents, preservative, auxiliary agents) as disclosed in the present specification (e.g. see specification pages 14-16 and examples).

Accordingly, the Bakaysa, DeFilippis and/or Balschmidt references taken separately or in combination provide an illustration of the conventional means of formulating pharmaceutical compositions comprising the Drejer insulin analogs including AspB28 which is extrapolatable to AspB25 insulin analog. It is also noted that these references provide further motivation to formulate pharmaceutical compositions comprising Asp B25 in light of the Drejer reference teaching the capability of both AspB25 and Asp B28 being fast-acting insulin analogs and with the Bakaysa/DeFilippis/Balschmidt teaching of making/testing Asp B28 for its fast action and long duration.

Thus, it would have been prima facie obvious to one of ordinary skill in the art, further in view of the Bakaysa, DeFilippis and/or Balschmidt reference, to make pharmaceutical compositions comprising the Drejer insulin analogs, including AspB25,

in amounts (an amount effective for said treating or ameliorating (type I diabetes)) within the scope of the presently claimed invention.

Discussion

Applicant's argument directed to the anticipation rejection over the Drejer reference was considered but deemed nonpersuasive regarding the above obviousness rejection over the same reference for the following reasons.

Applicant argues that "in Drejer et al. there is not a single reference to the possibilities of therapeutic use of any of the analogues" and that the "Examiner has taken Drejer's words out of context" (referring to page 1494).

This argument is not persuasive since it fails to consider the reference teaching as a whole to one of ordinary skill in the art. The Drejer reference, in various portions (e.g. abstract; pages 1488 and 1494 etc.) clearly teaches the expected in vivo activity (e.g. as fast-acting insulin analogs) of the Drejer reference insulin analogs in light of its experimental results. Additionally, the in vivo utility of the AspB28 Drejer analog confirmed by the Bakaysa/DeFilippis/Balschmidt references provides further motivation to make pharmaceutical compositions comprising the Drejer AspB25 insulin analog in amounts within the scope of the presently claimed invention.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Future Correspondences

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 571-272-0807. The examiner can normally be reached on 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-273-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bennett Celsa
Primary Examiner
Art Unit 1639

BC
April 20, 2004